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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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21005	7590	07/01/2005	EXAMINER	
HAMILTON, BROOK, SMITH & REYNOLDS, P.C. 530 VIRGINIA ROAD P.O. BOX 9133 CONCORD, MA 01742-9133			GAMBEL, PHILLIP	
			ART UNIT	PAPER NUMBER
			1644	

DATE MAILED: 07/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/010,229	LE ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 08 April 2005.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1,3-5 and 7-21 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3-5 and 7-21 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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### DETAILED ACTION

1. Applicant's amendment, filed 4/8/05, has been entered.

Claims 2 and 6 have been canceled.

Claims 1, 3-5, 7-8 and 11-13 have been amended

Claims 1-21 have been added.

Claims 1, 3-5 and 7-21 are pending.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.

This Action will be in response to applicant's arguments, filed 4/8/05.

The rejections of record can be found in the previous Office Action, mailed 10/6/04.

3. Applicant's assertions concerning priority of the instant application have been fully considered but are not found convincing essentially for the reasons of record.

Applicant relies upon "TNF- $\alpha$ -mediated human diseases", including "acute and chronic diseases" and "neoplastic disease", to support the recitation of "myelodysplastic syndrome" or "TNF- $\alpha$ -mediated myelodysplastic syndrome", as currently claimed.

It is acknowledged that the mechanism of treatment via TNF- $\alpha$ -specific antibodies would be the same regardless of the TNF- $\alpha$ -mediated disease in the context of neutralizing TNF- $\alpha$ -mediated inflammation.

However, as applicant admits, USSNs 07/853,606 and 07/943,852 do not provide specific examples directed to TNF- $\alpha$ -mediated myelodysplastic syndrome (see page 19, paragraph 2 of applicant's amendment, filed 4/8/05).

However, the issue of priority and new matter below is concerned with the written description of the diseases or conditions targeted in the claimed methods.

The instant claims now recite limitations which were not clearly disclosed in the priority applications as well as the specification as-filed, and would have changed the scope of the priority applications and do change the scope of the instant disclosure as-filed.

Neither the priority applications nor the instant application have provides a sufficient description of a representative number of species to represent the entire genus of "myelodysplastic syndrome" or "TNF- $\alpha$ -mediated myelodysplastic syndrome", as currently claimed.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Therefore, reliance upon the genus of "TNF- $\alpha$ -mediated human diseases" including "acute and chronic diseases" and "neoplastic disease" does not support the recitation of "myelodysplastic syndrome" or "TNF- $\alpha$ -mediated myelodysplastic syndrome", as currently claimed.

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It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

The filing date of the instant claims is deemed to be the filing date of the priority application USSN 08/192,093, filed 2/4/94 with respect to "myelodysplastic syndrome".

In addition, while applicant asserts that entitlement of priority should be granted for priority application USSN 07/670,827 equivalent to that of the disclosure of applicant's own prior art of record Le et al. (WO/16553).

Applicant is reminded that priority and written description differ from prior art determinations.

Also, applicant is reminded that a species reads on a genus.

Therefore, prior art referenced methods of treating myelodysplastic syndrome with anti-TNF  $\alpha$ -specific antibodies in view of Verhoef et al. (Leukemia 6: 1268 – 1272, 1992) in view of Le et al. (WO 92/16553) renders obvious the claimed methods.

Applicant's arguments concerning priority of the instant claims, drawn to "myelodysplastic syndrome" or "TNF- $\alpha$ -mediated myelodysplastic syndrome" have not been found persuasive.

Again, if applicant desires priority prior to the instant application, applicant is invited to point out and provide documentary support for the priority of the instant claims.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

5. Claims 1, 3-5 and 7-21 are 1, 3-5, 7-12 and 14-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

It is apparent that the  $\alpha$ 2 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line / hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

Applicant's arguments and comments, filed 4/8/05, concerning the enablement of the  $\alpha$ 2 antibody is acknowledged.

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Declarant Vilcek's indication that there was a policy of New York University to furnish third parties with a sample of the starting material A2 antibody (see Vilcek Declaration filed under 37 CFR 1.132, filed 4/8/05) is acknowledged.

However, biological materials must be known and readily available to the public (See MPEP 2404.01). Neither concept alone is sufficient. The fact that applicant and other members of the public were able to obtain the materials in question from a given source (e.g. New York University or a recognized depository) prior to and after the filing date of the application does not establish the upon issuance of a patent on the application that such material would continue to be accessible to the public. The applicant did not make of record any of the facts and circumstances surrounding the access to the biological materials from the depository, nor is there any evidence as to the depository's policy regarding the material if a patent would be granted. Further, there are no assurances that New York University would allow unlimited access to the material if the application has matured into a patent. Also, it is noted that the claims are drawn to the particular chimeric cA2 antibody and not the mouse A2 antibody.

In the absence of evidence that the cA2 antibody is readily available to the public and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, applicant's arguments are not persuasive and the rejection would be maintained.

It is noted that it is unclear if a cell line which has the exact structural and chemical identity of the cA2 antibody can be reproducibly isolated without undue experimentation. Replication of the claimed chimeric cA2 antibody is an unpredictable event. Further, a particular biological material or cell line can undergo changes resulting in microheterogeneity. Therefore, a suitable deposit or alternative means for patent purposes is required. Without a publicly available deposit of the appropriate cell line for the claimed cA2 antibody, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed.

As indicated previously, given the disclosure and the claims encompassing the instant cA2 antibody set forth in U.S. Patent No. 5,919,452; the conditions for the enablement of biological materials under 35 USC 112, first paragraph, with respect to cA2 appear to have been satisfied.

However in the interest of clarity and compact prosecution, again applicant is required to make the record clear exactly what is the scope of the instantly claimed cA2.

It is noted that the requirements under 35 USC 112, first paragraph, for the claimed cA2 antibody was not satisfied by the deposit of the cA2 antibody in the priority applications, some of which are patented now.

However, the instant record should indicate the parameters that have satisfied the enablement requirements under 35 USC 112, first paragraph, for the cA2 antibody.

6. Applicant's amended claims in conjunction with applicant's arguments, filed 4/8/05 have obviated the previous rejections under 35 U.S.C. 112, first paragraph, enablement, with respect to the "TNF- $\alpha$  specificity" and "TNF- $\alpha$ -mediated myelodysplastic syndrome".

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7. Claims 1, 3-5 and 7-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1, 3-5 and 7-21 are indefinite in the recitation of "cA2" because its characteristics are not known. The use of "cA2" monoclonal antibody as the sole means of identifying the claimed antibody renders the claim indefinite because "cA2" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct hybridomas / cell lines.

Applicant is invited to clarify the metes and bounds of the claimed cA2 antibody.

Applicant's arguments and comments, filed 4/8/05, have been fully considered concerning the indefiniteness of the instant "cA2".

However in the interest of clarity and compact prosecution, again applicant is required to make the record clear exactly what is the metes and bounds of the instantly claimed cA2.

As indicated previously and above,  
given the disclosure and the claims encompassing the instant cA2 antibody set forth in U.S. Patent No. 5,919,452; the conditions for the enablement of biological materials under 35 USC 112, first paragraph, with respect to cA2 appear to have been satisfied.

Applicant is invited to clarify the instant record.

It is noted that the requirements under 35 USC 112, first and second paragraphs, for the claimed cA2 antibody have been satisfied in the priority applications, some of which are patented now.

However, the instant record should indicate the parameters that have satisfied the requirement under 35 USC § 112, second paragraph as well as the enablement requirements under 35 USC 112, first paragraph, for the cA2 antibody.

B) Claims 11 and 14-15 are indefinite in the recitation of "neutralizing epitope of human TNF $\alpha$ " thereof because the claims fails to state sufficient structure and/or function which is to be achieved that defines the metes and bounds of the "neutralizing epitope of human TNF $\alpha$ ", which renders the claims indefinite. The phrase does not define the claimed "neutralizing activity" nor the structure of the claimed "neutralizing epitope" and the specification does not provide a standard for ascertaining the requisite definition of "neutralizing epitopes", and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Applicant is invited to amend the claims to clarify that the nature and metes and bounds of the claimed "neutralizing epitope of human TNF $\alpha$ ".

C) Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

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8. Claims 1, 3-5 and 7-21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Verhoef et al. (Leukemia 6: 1268 – 1272, 1992) in view of Le et al. (WO 92/16553) essentially for the reasons of record.

Applicant's arguments, filed 4/8/05, have been fully considered but are not found convincing essentially for the reasons of record.

As indicated above, applicant's assertions concerning priority of the instant claims have been fully considered, but have not been found convincing. Therefore the prior art stands as prior art.

In addition, applicant's efforts to argue unexpected results are not found convincing in view of the prior art Le et al. (WO 92/16553), which teaches the same advantages of the cA2 anti-TNF- $\alpha$  antibody as currently claimed.

The following of record is reiterated for applicant's convenience.

Verhoef et al. teach the therapeutic intervention of TNF- $\alpha$  with agents such as anti-TNF- antibodies in the treatment of anemias observed in myelodysplastic syndrome (see entire document, particularly page 1271, column 2, last sentence).

Verhoef et al. differs from the claimed invention by not disclosing the particular anti-TNF-  $\alpha$  cA2 specificity.

Le et al. teach the cA2 anti-TNF- $\alpha$  antibody, including the chimeric cA2 anti-TNF-  $\alpha$  antibody as well as its therapeutic use in subjects having pathologies and conditions associated with TNF-  $\alpha$  (See entire document, including the Summary of the Invention and Detailed Description of the Invention, including page 34, paragraph 1). ). Also see pages 34-38 for the well known dosing and modalities of administering therapeutic antibodies of interest to meet the needs of the patients as well as the Examples for affinity constants of prior art cA2-specific antibodies.

Although Verhoef et al. and Le et al. do not disclose humanized and human antibodies per se as therapeutic antibodies, one of ordinary skill in the art at the time the invention was made was motivated to make and use humanized and human antibodies in treating humans, given their well known advantages of their lower immunogenicity when compared to therapeutic antibodies which comprised non-human elements (e.g. murine monoclonal antibodies)

Therefore it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching so Le et al. to those of Verhoef et al. to obtain antagonistic TNF-  $\alpha$ -specific antibodies, including those with the cA2 specificity to counter the negative effects of TNF-  $\alpha$  in myelodysplastic syndrome. According to Verhoef et al., a person of ordinary skill in the art would have been motivated to administer anti-TNF-  $\alpha$  antibodies to counter the involvement of TNF  $\alpha$  in the pathogenesis of anemias in myelodysplastic syndrome (See Abstract and Discussion). Le et al. provides for antagonistic anti-TNF- $\alpha$  antibodies, including recombinant antibodies that are less immunogenic than murine monoclonal antibodies in therapeutic modalities involving humans. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of

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success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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June 20, 2005